IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

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First Named Inventor	BROWN, PATRICK
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Group Art Unit	1634
Examiner Name	FORMAN, BETTY J.
Title: *"MICROARRAYS OF POLYPEPTIDES"*	

Commissioner for Patents
PO Box 1450
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BRIEF ON APPEAL

REAL PARTY IN INTEREST

The real parties in interest are The Board of Trustees of the Leland Stanford Junior University, to which all rights have been assigned by the inventors, as evidenced by the assignments recorded on August 7, 2000, reel/frame 011119/0100.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on April 14, 2000 with Claims 1-30. During the course of prosecution, Claims 31-40 were added and Claims 1-9, 11, 12, 17, 19-30, 32 and 38-40 were canceled. Accordingly, Claims 10, 13-16, 18, 31 and 33-37 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

In response to the Restriction Requirement of June 6, 2001, Claims 10-18 (Group II) were elected for examination with traverse and argument for rejoinder of Claims 1-9 (Group I) for examination of Claims 1-18.

In response to the first Office Action of December 12, 2001, Claims 1, 10-16 and 18-19 were amended, Claims 8, 17 and 30 were canceled, Claims 31-37 were added and Group II was elected for examination with traverse and request for rejoinder of Claims 19-30 (Group III) and Group I and with Group II upon allowance.

In response to the Office Action of November 6, 2002, Claims 1-9 were withdrawn, Claims 11-12, 19-30 and 32 were canceled, Claims 10 and 31 were amended and new Claims 38-40 were added.

In response to the Final Office Action of August 13, 2003, Claims 1-9, 11-12, 17, 19-30 and 32 were canceled and Claims 31 and 36 were amended.

In response to the Office Action of September 19, 2005, Claims 10 and 31 were amended and Claim 10 rewritten in independent form.

In response to the Final Office Action of March 30, 2006, Claims 10 and 31 were amended. The Advisory Action of July 14, 2006 noted that these amendments would not be entered on appeal, and therefore Appellants have proceeded with the claims as presented in the response of September 19, 2005.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a microarray of discrete selected, distinct polypeptides on a slide, where each polypeptide is of at least 50 amino acids in length, and the microarray includes 1000 or more discrete regions of selected, distinct polypeptide per cm^2 of slide upon which discrete regions have a diameter of from 20 to 200 μm.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 10 claims a microarray of discrete selected, distinct polypeptides on a slide, in which each polypeptide is of at least 50 amino acids in length (page 5, line 3), in which the microarray includes 1000 or more discrete regions (page 4, line 30) of selected, distinct polypeptide per cm^2 of slide in which discrete regions have a diameter of from 20 to 200 μm (page 10, lines 21-23), produced by the method of:

(a) loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus (page 3, lines 19-22),

(b) tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support (page 10, lines 3-4), and

(c) repeating steps (a) and (b) until the microarray is formed (page 3, lines 17-18; page 5, line 3; page 7, line 2; page 10, lines 19-20; page 3, lines 18-29, page 8, lines 4-7; page 9, lines 13-20; page 10, lines 3-5; and page 11, lines 3-6).

Claim 13 claims the microarray of polypeptides according to Claim 10, in which the polypeptides are immunological receptors (page 6, lines 2-5).

Claim 14 claims the microarray of polypeptides according to Claim 13, in which the immunological receptors are antibodies (page 6, line 4).

Claim 15 claims the microarray of polypeptides according to Claim 10, in which the polypeptides are antigens (page 17, line 20).

Claim 16 claims the microarray of polypeptides according to Claim 10, in which the planar solid support includes a cationic film which binds the polypeptide (page 4, lines 2-6).

Claim 18 claims the microarray of polypeptides according to Claim 10, in which the polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure (page 5, lines 23-26).

Claim 31 claims a microarray of discrete selected, distinct polypeptides on a slide, in which each polypeptide is of at least 50 amino acids in length and in which the microarray includes 1000 or more discrete regions of selected, distinct polypeptide per cm^2 of slide, and in which discrete regions have a diameter of from 20 to 200 μm (page 3, lines 17-18; page 5, line 3; page 7, line 2; and page 10, lines 19-20).

Claim 33 claims the microarray of polypeptides according to Claim 31, in which the polypeptides are immunological receptors (page 6, lines 2-5).

Claim 34 claims the microarray of polypeptides according to Claim 33, in which the immunological receptors are antibodies (page 6, line 4).

Claim 35 claims the microarray of polypeptides according to Claim 31, in which the polypeptides are antigens (page 17, line 20).

Claim 36 claims the microarray of polypeptides according to Claim 31, in which the slide includes a cationic film which binds the polypeptide (page 4, lines 2-6).

Claim 37 claims the microarray of polypeptides according to Claim 31, in which the polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure (page 5, lines 23-26).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 31 and 33-37 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Winkler *et al.* (U.S. Patent No. 5,677,195 filed 20 November 1992).

II. Claims 10, 13-15, 18, 31 and 33-37 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Barrett *et al.* (U.S. Patent No. 5,252,743 filed 13 November 1990).

III. Claims 10, 13-15, 18, 31 and 33-35 stand rejected under 35 U.S.C. § 103(a) as being anticipated by Beattie (U.S. Patent No. 5,843,767, filed 10 April 1996) as defined by Zubay, G. (Biochemistry, 3rd ed., Wm C. Brown Pub., Dubuque Iowa, 1993, pages 964-966) in view of Chang (U.S. Patent No. 4,829,010, filed May 9 1989).

IV. Claims 16 and 36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie as defined by Zubay in view of Chang as applied above, and further in view of Van Ness *et al.*

V. Claims 16 and 36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett *et al.* (U.S. Patent No. 5,353,743, filed 13 November 1990) in view of Van Ness *et al.* (U.S. Patent No. 5,667,976, filed 14 February 1996).

ARGUMENT

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows. The groups are appropriate, in that rejections I, IV and V are applied only to specific claims. Further, for purposes of prior art, Claims 13-15, 33-35 and 37 provide for specific proteins, e.g. immunological receptors are antigens, which proteins have a function that cannot be provided by the very short peptides taught in the prior art. The, independent grouping is appropriate.

Group I: Claim 10, drawn to a microarray of discrete selected, distinct polypeptides on a slide, in which each polypeptide is of at least 50 amino acids in length, in which the microarray includes 1000 or more discrete regions of selected, distinct polypeptide per cm^2 of slide in which discrete regions have a diameter of from 20 to 200 μm, produced by the method of loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus, tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support, and repeating until the microarray is formed.

Group II: Claims 13-15 and 18, drawn to a microarray of Claim 10 in which the polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure, in which the polypeptides are immunological receptors including antibodies, or in which the polypeptides are antigens.

Group III: Claim 16, drawn to a microarray of Claim 10 in which the planar solid support includes a cationic film which binds the polypeptide.

Group IV: Claim 31, drawn to a microarray of discrete selected, distinct polypeptides on a slide, in which each polypeptide is of at least 50 amino acids in length, in which the microarray includes 1000 or more discrete regions of selected, distinct polypeptide per cm^2 of slide in which discrete regions have a diameter of from 20 to 200 μm.

Group V: Claim 33-35 and 37, drawn to a microarray of Claim 31 in which the polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure, in which the polypeptides are immunological receptors including antibodies, or in which the polypeptides are antigens.

Group VI: Claim 36, drawn to a microarray of polypeptides according to Claim 31, in which the slide includes a cationic film which binds the polypeptide.

I. Claims 31 and 33-37 are not anticipated under 35 U.S.C. § 102(e) by Winkler *et al.* (U.S. Patent No. 5,677,195 filed 20 November 1992).

Groups IV, V and VI: Claims 31 and 33-37

The Winkler *et al.* patent is directed to methods of synthesizing polymers *in situ* on a substrate, where only small peptides can be produced, and thus does not teach the invention set forth in Claims 31 and 33-37.

The methods of Winkler *et al.* relate to the synthesis of polymers on a substrate, and can not be adapted to provide the microarrays taught by Appellants. As stated in the summary of the Winkler *et al.* invention:

> According to the first specific aspect of the invention, a block having a series of channels, such as grooves, on a surface thereof is utilized. The block is placed in contact with a derivatized glass or other substrate. In a first step, a pipettor or other delivery system is used to flow selected reagents to one or more of a series of apertures connected to the channels, or place reagents in the channels directly, filling the channels and "striping" the substrate with a first reagent, coupling a first group of monomers thereto. The first group of monomers need not be homogenous. For example, a monomer A may be placed in a first group of the channels, a monomer B in a second group of channels, and a monomer C in a third group of channels. The channels may in some embodiments thereafter be provided with additional reagents, providing coupling of additional monomers to the first group of monomers. The block is then translated or rotated, again placed on the substrate, and the process is repeated with a second reagent, coupling a second group of monomers to different regions of the substrate. The process is repeated until a diverse set of polymers of desired sequence and length is formed on the substrate. By virtue of the process, a number of polymers having diverse monomer sequences such as peptides or oligonucleotides are formed on the substrate at known locations.

This method of *in situ* synthesis of the polymer is further supported by the citations to the patent provided in the Office Action of September 19, 2005. It is stated in the Office Action that the patent teaches an array comprising 1000 or more discrete regions of distinct polypeptides/cm^2 at column 17, lines 49-58. However, the cited section cannot be understood in isolation, as the preceding paragraphs explain the invention in more detail. Specifically, it can be seen from the preceding columns that the described invention relates to the synthesis of polymers *in situ*.

A particularly preferred channel block is prepared by chemical etching of polished silicon wafers. Chemical etching is a widely used technique in integrated circuit fabrications. It can easily provide 60 or more 100 micron channels on a 12.8 mm region of a polished silicon wafer. Even after etching, the top (unetched) surface regions of the wafer retains the very flat profile of the unetched wafer. Thus, close contact with the substrate is ensured during flow cell operation.

In operation, the surface of the substrate is appropriately treated by cleaning with, for example, organic solvents, methylene chloride, DMF, ethyl alcohol, or the like. Optionally, the substrate may be provided with appropriate linker molecules on the surface thereof. The linker molecules may be, for example, aryl acetylene, ethylene glycol oligomers containing from 2–10 monomers or more, diamines, diacids, amino acids, or combinations thereof. Thereafter, the surface is provided with protected surface active groups such as t-butoxycarbonyl (TBOC) or 9-fluorenylmethoxycarbonyl ("FMOC") protected amino acids. Such techniques are well known to those of skill in the art.

Thereafter, the channel block and the substrate are brought into contact forming fluid-tight channels bounded by the grooves in the channel block and the substrate. When the channel block and the substrate are in contact, a protecting group removal agent is, thereafter, directed through a first selected channel or group of channels by placing the pipettor on the flow inlet of the selected channel and, optionally, the vacuum source on the outlet of the channel. In the case of, for example, TBOC protected amino acids, this protecting group removal agent may be, for example, trifluoroacetic acid (TFA). This step is optionally followed by steps of washing to remove excess TFA with, for example, dichloromethane (DCM).

Thereafter, a first amino acid or other monomer A is directed through the first selected flow channel. Preferably this first amino acid is also provided with an appropriate protecting group such as TBOC, FMOC, nitroveratryloxycarbonyl ("NVOC"), or the like. This step is also followed by appropriate washing steps. The of deprotection/coupling steps employed in the first group of channels are concurrently with or thereafter repeated in additional groups of channels. In preferred embodiments, monomer A will be directed through the first group of channels, monomer B will be directed through a second group of flow channels, etc., so that a variety of different monomers are coupled on parallel channels of the substrate.

Thereafter, the substrate and the channel block are separated and, optionally, the entire substrate is washed with an appropriate material to remove any unwanted materials from the points where the channels contact the substrate.

The substrate and/or block is then, optionally, washed and translated and/or rotated with the stage. In preferred embodiments, the substrate is rotated 90 degrees from its original position, although some embodiments may provide for greater or less rotation, such as from 0 to 180 degrees. In other embodiments, such as those discussed in connection with the device shown in FIG. 7, two or more different channel blocks are employed to produce different flow patterns across the substrate. When the channel block is rotated, it may simultaneously be translated with respect to the substrate. "Translated" means any relative motion of the substrate and/or channel block, while "rotation" is intended to refer to rotation of the substrate and/or channel block about an axis perpendicular to the substrate and/or channel block. According to some embodiments the relative rotation is at different angles for different stages of the synthesis.

The steps of deprotection, and coupling of amino acids or other monomers is then repeated, resulting in the formation of an array of polymers on the surface of the substrate. For example, a monomer B may be directed through selected flow channels, providing the polymer AB at intersections of the channels formed by the channel block in the first position with the channels formed by the channel block after 90-degree rotation.

While rotation of the channel block is provided according to preferred embodiments of the invention, such rotation is not required. For example, by simply flowing different reagents through the channels, polymers having different monomer sequences may be formed. Merely by way of a specific example, a portion of the channels may be filled with monomer "A," and a portion filled with monomer "B" in a first coupling step. All or a portion of the first channels are then filled with a monomer "C," and all or a portion of the second channels are filled with a monomer "D," forming the sequences AB and CD. Such steps could be used to form 100 sequences using a basis set of 10 monomers with a 100-groove channel block.

In another embodiment, the invention provides a multichannel solid-phase synthesizer as shown in FIG. 12. In this embodiment, a collection of delivery lines such as a manifold or collection of tubes **1000** delivers activated reagents to a synthesis support matrix **1002**. The collection of tubes **1000** may take the form of a rigid synthesis block manifold which can be precisely aligned with the synthesis support matrix **1002**. The support matrix contains a plurality of reaction regions **1004** in which compounds may be immobilized or synthesized. In preferred embodiments, the reaction regions include synthesis frits, pads, resins, or the like.

The solutions delivered to the individual reactant regions of the support matrix flow through the reaction regions to waste disposal regions, recycling tank(s), separators, etc. In some embodiments, the reaction solutions simply pass through the reaction regions under the influence of gravity, while in other embodiments, the solutions are pulled or pushed through the reaction regions by vacuum or pressure.

The individual reaction regions **1004** of the support matrix are separated from one another by walls or gaskets **1006**. These prevent the reactant solution in one reaction region from moving to and contaminating adjacent reaction regions. In one embodiment, the reaction regions are defined by tubes which may be filled with resin or reaction mixture. The gasketing allows close contact between the support matrix **1002** and a "mask" (not shown). The mask serves to control delivery of a first group reactant solutions through predetermined lines (tubes) to a first set of reaction regions. By ensuring close contact between the delivery tubes **1000**, the mask, and the support matrix **1002**, the probability that reaction solutions will be accidently added to the wrong reaction site is reduced.

After each process step, the mask can be changed so that a new group reactants is delivered to a new set of reaction regions. In this manner, a combinatorial strategy can be employed to prepare a large array of polymers or other compounds. In other embodiments, mechanisms other than masks can be employed to block the individual delivery tubes. For example, an array of control valves within the tubes may be suitable for some embodiments.

By adjusting the thickness of the synthesis support matrix, the quantity of immobilized material in the reaction regions can be controlled. For example, relatively thin support synthesis matrices can be used to produce small amounts of surface bound oligomers for analysis, while thicker support matrices can be used to synthesize relatively large quantities

In fact, the overlapping nature of the circles and channels described by Winkler *et al.* are well suited for synthetic methods, where the overlapping monomers provide for combinatorial libraries, but are not suited for the deposition of a single polypeptide. Such intersections of previous or subsequent channels (which are the means by which multiple, distinct, polymers are synthesized) would introduce undesirable contamination for the deposition of long polypeptides.

of oligomers which can be cleaved from the support for further use. In the latter embodiment, a collector having dimensions matching the individual synthesis supports can be employed to collect oligomers that are ultimately freed from the reaction matrix.

To illustrate the ability of this system to synthesize numerous polymers, a square synthesis matrix measuring 10 cm along each side and having 5 mm reaction regions separated by 5 mm wide gaskets provides 100 individual syntheses sites (reaction regions). By reducing the size of the reaction regions to 2.5 mm on each side, 400 reactions regions become available.

While linear grooves are shown herein in the preferred aspects of the invention, other embodiments of the invention will provide for circular rings or other shapes such as circular rings with radial grooves running between selected rings. According to some embodiments, channel blocks with different geometric configurations will be used from one step to the next, such as circular rings in one step and linear stripes in the next. FIG. 13*a* illustrates one of the possible arrangements in which the channels **409** are arranged in a serpentine arrangement in the channel block **407**. Through appropriate translation and/or rotation of the channel block, polymers of desired monomer sequence are formed at the intersection of the channels during successive polymer additions, such as at location **501**, where the intersection of a previous or subsequent set of channels is shown in dashed lines. FIG. 13*b* illustrates another arrangement in which channels (in this case without flow paths **413**) are provided in a linear arrangement, with groups **503** and **505** located in adjacent regions of the substrate and extending only a portion of the substrate length.

In some embodiments of the invention, the various reagents, such as those containing the various monomers, are not pumped through the apertures **413**. Instead, the reagent is placed in one of the grooves, such as the grooves **409** shown in FIG. 13*b*, filling the groove. The substrate is then placed on top of the channel block, and the exposed portions of the substrate are permitted to react with the materials in the grooves. In preferred embodiments, the channels are of the same width as the raised regions between the channels. According to these embodiments, the substrate may then be moved laterally by one channel width or an integer multiple of a channel width, permitting reaction with and placement of monomers on the regions between the channels in a previous coupling step. Thereafter, the substrate or channel block will be rotated for the next series of coupling steps.

In preferred embodiments, the process is repeated to provide more than 10 different polymer sequences on the surface of the substrate. In more preferred embodiments, the process is repeated to provide more than 10^2, 10^3, 10^4, 10^5, 10^6, or more polymer sequences on a single substrate. In some embodiments the process is repeated to provide polymers with as few as two monomers, although the process may be readily adapted to form polymers having 3, 4, 5, 6, 10, 15, 20, 30, 40, 50, 75, 100 or more monomers therein.

It can clearly be seen that the context of col. 17, lines 49-58 refers to the process of synthesizing polymers on a substrate, varying the position and composition of monomers, in order to achieve a desired density of spots. However, such methods are not applicable to polypeptides of greater than at least 50 amino acids in length.

As was discussed in Appellants' response of June 11, 2002, polypeptides of at least 50 amino acids in length cannot be synthesized *in situ* to provide for a distinct spot of a single peptide. The research article Fodor *et al* (*Science* 251:767-773, 1991), previously provided, describes the method of reacting monomers on a substrate surface to generate polymers. The Fodor paper shows light directed synthesis of two pentapeptides YGGFL and PGGFL on the surface of a substrate, shows that the peptides have been correctly synthesized, and further shows a ten-step binary synthesis of peptides of a range of sizes, up to 10 amino acids in length.

Fodor, on page 771, second paragraph of the first column states: "The net coupling yield *per cycle* in these experiments is typically between 85 and 95 percent." and further recites, in reference 9, the rigorous methods that were used to derived these figures. Therefore, each time a residue is added to a growing polypeptide chain using this method, it is added with an efficiency of 85-95%.

For the purposes of the following discussion, it will be assumed that the coupling efficiency of each cycle is 90%, the average of 85% and 95%. Using the above information, simple algebra teaches that the synthesis of a polypeptide using these methods becomes less and less efficient. For example, assuming the first amino acid is coupled to the substrate is 100% efficient, the synthesis of a two-mer polypeptide will be 90% efficient, the synthesis of a four-mer polypeptide will be 73% (0.9 x 0.9 x 0.9), the synthesis of a 10-mer polypeptide will be 34% (i.e. 0.9^{9}), the synthesis of a 20-mer polypeptide will be 13% (i.e. 0.9^{19}) efficient, the synthesis of a 35-mer polypeptide will be 2.5% (i.e. 0.9^{34}) efficient, and the synthesis of a 50-mer polypeptide will be 0.5% (i.e. 0.9^{49}) efficient. Thus, using an average of 90% coupling efficiency, if a 50-mer is synthesized using the in situ synthesis method, only 0.5% of the polypeptides will have the correct sequence. In other words, synthesis of a 50-mer using this method will result in a heterogeneous mixture of polypeptides, only 5 molecules in a 1000 of which will have the correct sequence.

At this level, the method ceases to be functional, and is no longer useful for synthesizing a selected polypeptide onto a substrate. This effect is demonstrated in the Fodor paper, in which it is noted that no polypeptide of over 7 residues in length was highly bound by a specific

antibody (page 771, second column, second paragraph), despite at least one of the polypeptides having a sequence that should have bound to the antibody.

The Office Action of September 19, 2005 states that Winkler *et al.* teach that the peptides are antibodies or antigens. Appellants respectfully submit that Winkler *et al.* teach that antibodies can be objects of study by the methods of the invention, not that antibodies are provided in a microarray format. The cited section of the patent is under the heading that reads "Specific examples of receptors which can be investigated by this invention". The further discussion of antibodies in the context of the Winkler invention clearly demonstrates how they are used (col. 17, line 58 to col. 18, line 6):

> According to preferred embodiments, the array of polymer sequences is utilized in one or more of a variety of screening processes, one of which is described in copending application U.S. Ser. No. 796,947, filed on Nov. 22, 1991 and incorporated herein by reference for all purposes. For example, according to one embodiment, the substrate is then exposed to a receptor of interest such as an enzyme or antibody. According to preferred embodiments, the receptor is labelled with fluorescein, or otherwise labelled, so as to provide for easy detection of the location at which the receptor binds. According to some embodiments, the channel block is used to direct solutions containing a receptor over a synthesized array of polymers. For example, according to some embodiments the channel block is used to direct receptor solutions having different receptor concentrations over regions of the substrate.

It is clearly understood by one of the skill in the art that antibodies or other receptors are brought into contact with an array of polymer sequences; the antibodies are not the polymers of the sequence. This follows directly from the above discussion of the inefficiency of synthesizing polypeptides *in situ*. Antibodies are large, complex multimeric proteins, containing multiple disulfide linkages. One of skill in the art cannot synthesize an array of functional antibody molecules on a substrate using the methods taught by Winkler *et al.* The skilled artisan readily understands that the sole method of arriving at a distinct, selected polypeptide, where this may include molecules such as immunoglobulins or immunological receptors, is by the isolation of the native proteins. At the time of filing and since, the *in situ* synthesis of any such molecule is well beyond the capacity of the art to achieve.

In reply to arguments made in Appellant's response of 13 January, 2006 and reiterated the response of June 28, 2006, the Examiner asserts that they are not persuasive because the

present "claims are drawn to a microarray having polypeptides of at least 50 amino acids", adding that the "claims do not define or limit the sequence of the polypeptides such that the "correct sequence" is provided" (Office Action of March 30, 2006, page 3). Appellants respectfully submit that the present claims are directed to a microarray of regions of distinct polypeptide on a slide, wherein each polypeptide is of at least 50 amino acids in length.

Appellants note that the claims refer to the use of a "distinct polypeptide" at each region, and that each spot on the microarrays as claimed therefore refers to a specific polypeptide that has been selected for deposition on the array, as detailed in the specification. In contrast, the methods of Winkler *et al.* cannot provide for a distinct polypeptide, because the method of *in situ* synthesis always results in an aggregation of polypeptides of different sequences, the vast majority of which have randomly introduced errors in synthesis as reviewed above.

Accordingly, a reference which employs *in situ* synthesis as does Winkler *et al.* cannot under any circumstances provide regions of selected, distinct polypeptide of at least 50 amino acids in length, but only regions of mixed polypeptides containing a very small amount of the selected polypeptide, if any at all.

In reply to arguments made by Appellants in the Response of 13 January, 2006 showing that the teachings of Winkler *et al.* cannot produce regions of selected, distinct polypeptide on a slide, wherein each polypeptide is of at least 50 amino acids in length, the Examiner cites the treatment of product-by-process claims of record in *In re* Thorpe, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and states that "the claims are drawn to a product ... because the claims do not define the product over that of Winkler, the claims are not patentable over the prior art product" (Office Action of March 30, 2006, page 3).

Examiner's citation of *In re* Thorpe is not apposite to Appellants' argument. As reviewed above, Appellants distinguish the claims over the cited art by referring to a recited characteristic of the claimed product, namely, that it possesses "discrete regions of selected, distinct polypeptide." Appellants do indeed make reference to the process of Winkler *et al.*, because such a process is incapable of producing the claimed product.

Put simply, Appellant's argument rests upon demonstrating that the process taught in the cited reference is incapable of generating the claimed product, irrespective of any process disclosed by Appellants. Invoking *In re* Thorpe in order to exclude consideration of a process taught by Applicants is not a response to that argument.

Accordingly, applicants respectfully submit that the instantly claimed invention is readily distinguished over the prior art for reasons of record.

II. Claims 10, 13-15, 18, 31 and 33-37 are not anticipated under 35 U.S.C. § 102(e) by Barrett *et al.* (U.S. Patent No. 5,252,743 filed 13 November 1990).

Groups I, II, IV and V: Claims 10, 13-15, 18, 31, 33-35 and 37

The Examiner rejects Claims 10, 13-15, 18, 31 and 33-37 under 35 U.S.C. § 102(e) as being anticipated by Barrett et al. Applicants respectfully submit that the presently claimed invention is not anticipated by the cited reference.

Applicants respectfully submit that Barrett *et al.* fail to teach a cationic film on a solid support capable of binding peptide, as claimed in the present invention. It is well known that to support a claim of anticipation under 35 U.S.C. § 102(e), each and every element of the invention as claimed must be taught. Since Barrett et al. fail to teach each and every element of the claimed invention, Claims 10, 13-15, 18, 31 and 33-37 are not anticipated under 35 U.S.C. § 102(e) by Barrett et al. and this rejection may be withdrawn.

Since Barrett *et al.* fail to teach each and every element of the claimed invention, Claims 10, 13-15, 18, 31 and 33-37 are not anticipated under 35 U.S.C. § 102(e) by Barrett *et al.* Reversal of the rejection is requested.

III. Claims 10, 13-15, 18, 31 and 33-35 are not anticipated under 35 U.S.C. § 103(e) by Beattie (U.S. Patent No. 5,843,767, filed 10 April 1996) as defined by Zubay, G. (Biochemistry, 3rd ed., Wm C. Brown Pub., Dubuque Iowa, 1993, pages 964-966) in view of Chang (U.S. Patent No. 4,829,010, filed May 9 1989).

Groups I, II, IV and IV: Claims 10, 13-15, 18, 31 and 33-35

In response to the Office Action of September 19, 2005, and reiterated herein, Appellants note that the rejected claims recite that the microarray is created by loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus, and tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support such that it forms discrete regions with a diameter from 20-200 μm. The cited art fails to teach an array having the specific geometry set forth by Appellants.

Appellants note that the substrate of Beattie is not a solid planar surface, but a substrate comprising "a multiplicity of discrete channels", and where the binding reagent is not on the flat surface but on the walls of the channels, which are curved surfaces. As stated by Beattie, a "variety of materials can be immobilized or fixed to the glass surfaces within the channels of the NCG array, to yield a high surface area to volume ratio ", which is not found in a planar surface. The methods of Beattie *et al.* cannot teach a planar array having a defined diameter, because the arrays of Beattie *et al.* are immobilized or fixed to the channel walls, and thus are not a planar region.

Further, the microfluidic devices utilized in the methods of Beattie *et al.* do not deliver fluids by the tapping and deposition method recited in the present claims, but with a microfluidic jet (col. 14, lines 32-35). Such micro-jet devices operate by a different mechanism, and are not expected to generate the same array on a planar surface as arrays produced by the methods of the present invention. In fact, the methods of Beattie *et al.* utilize a flow-through vacuum system for binding DNA probes or targets (example 6), a modification that is not possible where the substrate is a non-porous slide. Because the microfluidic devices of Beattie *et al.* are utilized with a porous substrate, not a solid slide, one of skill in the art is not motivated to combine the microfluidic device with the teachings of Chang in order to achieve the presently claimed invention.

Further, Beattie *et al.* specifically teaches away from the use of flat, i.e. planar, substrates, stating that:

> "Another limitation of these prior art approaches is the fact that a flat surface design introduces a rate-limiting step in the hybridization reaction, i.e., diffusion of target molecules over relatively long distances before encountering the complementary probes on the surface. In contrast, the microfabricated apparatus according to the present invention is designed to overcome the inherent limitations in current solid phase hybridization materials, eliminating the diffusion-limited step in flat surface hybridizations and increasing the cross sectional density of DNA. "

The Office Action states that Beattie *et al.* teaches the use of a slide. Appellants respectfully disagree. Beattie *et al.* is clearly and resolutely directed to the use of a porous material having functional wells. The citation of Beattie in the Office Action reads as follows:

> Initial lamination process development is carried out using unablated polymeric material (or alternatively using glass slides and/or silicon wafers). Cure temperature,

pressure and fixturing are optimized during this process development. Thereafter, the optimized processing parameters are employed to laminate both nonporous wafers and polymeric arrays. The final lamination is done such that the alignment of the two layers creates functional wells.

One of skill in the art, upon reading the specification of Beattie *et al.*, can be in no doubt that the reference does not intend arrays to be produced on a flat surface, but rather on a microfabricated apparatus having numerous channels for binding of the DNA. Appellants respectfully submit that Beattie *et al.* does not teach microarrays on a slide – only that the arrays of the Beattie invention could utilize a slide in initial fabrication prior to creation of the wells that are central to the Beattie invention. Indeed, one need only read the title of the patent, "Microfabricated, Flowthrough Porous Apparatus for Discrete Detection of Binding Reactions" to understand that Beattie *et al.* does not teach microarrays on slides, but rather on a flow-through porous apparatus.

Beattie *et al.* does not – indeed, cannot - teach the dimensions of discrete regions taught by Appellants and specifically recited in the rejected claims, because Beattie *et al.* does not teach a planar array, but rather a perforated array wherein the sides of wells are coated with DNA.

Further, with respect to Claims 10, 13-15 and 18, Beattie *et al.* cannot teach a product produced by a method wherein a dispensing device taps the surface of a planar solid, since the substrate of Beattie *et al.* comprises wells, (i.e. an open space). It would thus be physically impossible to utilize the teachings of Beattie to derive a device whose production necessitates tapping the tip of the dispensing device against a surface of a planar solid support at a defined position.

Appellants respectfully submit that there is no reason to combine the teachings of Chang, which may utilize a slide, with the teachings of Beattie *et al.*, which specifically teach that a flat surface design is undesirable as shown above. The combination of the two references is clearly a case of hindsight – picking and choosing from disparate elements in order to spin together Appellants' invention, where the references themselves clearly do not suggest such combination.

One of skill in the art would read Beattie *et al.* as teaching a particular flow-through apparatus, in which a solution is sprayed into a well in order to provide a greater surface area for binding. Such teachings are not reasonably combined with the pipetting device of Chang *et al.*

In response to arguments presented by Appellants in the response of January 13, 2006, and reiterated herein, the Examiner maintains the assertion that "Beattie *et al* specifically teach a slide (Column 11, lines 40-42). While the reference does create nanoporous wells within the substrate, the substrate is a slide and therefore encompassed by the claimed 'slide'" (Office Action of March 30, 2006, page 9).

Appellants submit that the use of the term "slide" in the reference cited by the Examiner clearly substantiates a prohibited use of hindsight in making this determination of obviousness. The full context of the term cited from column 11 of Beattie *et al.* is reproduced below:

> Part B: Ablation tooling and processing
>
> Contact mask excimer laser machining is a preferred processing technique because it is a lower cost technique than projection mask excimer laser machining. A projection mask is, however, employed when the feature size less than 50 μm. One or more masks with a variety of pattern sizes and shapes are fabricated, along with fixtures to hold the mask and material to be ablated. These masks are employed to determine the optimal material for laser machining and the optimal machining conditions (i.e., mask hole size, energy density, input rate, etc.). Scanning electron microscopy and optical microscopy are used to inspect the excimer laser machined parts, and to quantify the dimensions obtained, including the variation in the dimensions.
>
> In addition to ablating the sample wells into the polymeric material, the adhesive material is also ablated. This second ablation is undertaken so that the diameter of the hole in the adhesive is made larger than diameter of the sample well on the adhesive side of the polymeric material. This prevents the adhesive from spreading into the sample well and/or the nanoporous glass during lamination.
>
> Part C: Lamination tooling and processing
>
> Initial lamination process development is carried out using unablated polymeric material (or alternatively, using glass slides and/or silicon wafers). Cure temperature, pressure, and fixturing are optimized during this process development. Thereafter, the optimized processing parameters are employed to laminate both nanoporous wafers and polymeric arrays. The final lamination is done such that the alignment of the two layers creates functional wells.

Appellants note that this is the only use of the term "slide" in the entirety of the reference, and it is used to denote one of the materials, among several of which could be chosen, to which function may be imparted in order to arrive at the product claimed by Beattie *et al.* The process taught by Beattie *et al.*, at its completion, "creates functional wells" for a flowthrough capacity

whose presence is required and in every case taught by Beattie *et al.* The Abstract of the cited reference indicates that, "The apparatus is characterized by discrete and isolated regions that extend through said substrate and terminate on a second surface thereof such that when a test sample is allowed to the substrate, it is capable of penetrating through each such region during the course of said binding reaction." It is thereby made plain to one of skill in the art that the device taught by Beattie *et al.* absolutely requires the presence of channels through the substrate, be it glass or silicon, in order to function. As discussed above, it is equally plain that the substrate taught by Beattie *et al.* cannot be functionally combined with a reference such as Chang teaching the binding of polypeptides to a planar surface, as the described product cannot function without wells which penetrate the substrate to allow flowthrough. A combination of references which results in an inoperable reference teaches away from that combination, supporting a showing of nonobviousness of the invention under examination. See *In re* Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Accordingly, the Examiner's argument that "the substrate [of Beattie *et al.*] is a slide and therefore encompassed by the claimed 'slide'" is without force. As discussed above, a substrate can have ablative polypeptide binding surfaces which penetrate and extend through it, thereby enabling the function of the product of Beattie *et al.* to the exclusion of the instantly claimed invention, or a substrate can present a surface upon which discrete regions of polypeptide with a particular defined diameter can be deposited, thereby enabling the function of the presently claimed invention to the exclusion of Beattie *et al.*. These conditions being mutually exclusive, they cannot both be encompassed by a claim drawn to a "slide" in the presence of other relevant limitations, as discussed. Applying the Examiner's logic, the claims of the present application would then be considered to infringe upon any patent wherein the use of a slide is taught for any purpose, or even to encompass a product consisting solely of a blank glass slide itself. As this is not the case, Applicants submit that the instant claims define the array over the nanoporous substrate of Beattie *et al.*

In the Advisory Action of July 14, 2006, the Examiner states that "Applicant asserts that Beattie cannot teach a planar array as claimed because they do not teach deposition via tapping". Applicants submit that this is a misstatement of Applicants' argument. Applicants maintain that Beattie *et al.* cannot teach a planar array as claimed because Beattie *et al.* do not teach a planar array at all, but a "flowthrough porous apparatus" whose function invariantly requires wells, not a planar surface.

Independently, as a result of this selection of substrate, Beattie *et al.* therefore cannot use an impact printing method, as claimed, but instead teach a non-impact, micro-jet printing

mechanism to deposit analyte. Such micro-jet devices operate by a different mechanism, and are not expected to generate the same array on a planar surface as arrays produced by the methods of the present invention. In fact, the methods of Beattie et al. utilize a flow-through vacuum system for binding DNA probes or targets (example 6), a modification that is not possible where the substrate is a non-porous slide. Because the microfluidic devices of Beattie et al. are utilized with a porous substrate, not a solid slide, one of skill in the art is not motivated to combine the microfluidic device with the teachings of Chang or Van Ness et al. in order to achieve the presently claimed invention.

The Examiner additionally states, without providing citation, that "Applicant asserts that the method used by Beattie *et al.* differs from the method of Claim 10," and that this is not persuasive because the process of making the product does not define it over the prior art.

Appellants have at no point in any communication sought to distinguish the claimed product over the prior art by distinguishing its method of production except where this is specifically relevant to the structure of the claimed product. The product as claimed is physically described by the method used to produce it, with resulting limitations upon the product itself. One argument made by Appellants highlights the fact that a product of Claim 10 cannot result from the teachings of Beattie *et al.* as it would be physically impossible to utilize those teachings to arrive at a device whose method of production involves tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, since the substrate of Beattie *et al.* comprises wells (i.e. an open space).

In response to Appellants' argument that one of skill in the art would not reasonably combine the porous substrate of Beattie *et al.* with the pipetting device of Chang, the Examiner states, in the Office Action of March 30, 2006, on page 9, that the art is analogous. The Appellants note, however, that the fact that the device of both references involves the immobilized binding of polymers does not remedy the structural differences which render these teachings unable to be operatively combined. The inkjet method employed by Beattie *et al.* and cited by the Examiner is indeed, as argued by the Appellants, a non-impact, contactless method of solution dispensing which is accurately described by Appellants as "spraying" and thereby contrasted with the pipetting method as employed by Chang. While both methods do indeed find uses in broadly analogous art, the structural divergence, namely that of incorporating a porous versus a planar surface, of the respective products renders the combination of the pipetting method of Chang and the substrate of Beattie *et al.* inoperable and substantiates the nonobviousness of the presently claimed invention.

Because Beattie *et al.* and Chang are silent with regard to loading a polypeptide solution into an elongate capillary channel and tapping its tip onto the support to dispense the solution therein in a precise amount and pattern, the Examiner seeks to base the previously made rejections upon the judicial precedent of *In re* Best (195 USPQ 430) and *In re* Fitzgerald (205 USPQ 594). However, the facts of *In re* Fitzgerald themselves illustrate precisely why the application of this precedent is invalid in the present case. According to MPEP section 2112:

> In *In re* Fitzgerald *et al.*, 205 USPQ 594 (CCPA 1980), the claims were directed to a self-locking screw-threaded fastener comprising a metallic threaded fastener having patches of crystallizable thermoplastic bonded thereto. The claim further specified that the thermoplastic had a reduced degree of crystallization shrinkage. The specification disclosed that the locking fastener was made by heating the metal fastener to melt a thermoplastic blank which is pressed against the metal. After the thermoplastic adheres to the metal fastener, the end product is cooled by quenching in water. The examiner made a rejection based on a U.S. patent to Barnes. Barnes taught a self-locking fastener in which the patch of thermoplastic was made by depositing thermoplastic powder on a metallic fastener which was then heated. The end product was cooled in ambient air, by cooling air or by contacting the fastener with a water trough. The court first noted that the two fasteners were identical or only slightly different from each other. "Both fasteners possess the same utility, employ the same crystallizable polymer (nylon 11), and have an adherent plastic patch formed by melting and then cooling the polymer." Id. at 596 n.1. The court then noted that the Board had found that Barnes' cooling rate could reasonably be expected to result in a polymer possessing the claimed crystallization shrinkage rate. Appellant had not rebutted this finding with evidence that the shrinkage rate was indeed different. They had only argued that the crystallization shrinkage rate was dependent on the cool down rate and that the cool down rate of Barnes was much slower than theirs. Because a difference in the cool down rate does not necessarily result in a difference in shrinkage, objective evidence was required to rebut the 35 U.S.C. 102/103 prima facie case.

Thus, in *In re* Fitzgerald, the invention under examination was met by a single reference in which an identical or near-identical product possessing the same utility was judged to be produced by a method with an inherent capacity to produce an object indistinguishable from the product under examination. In contrast, the present application is met by two references defined by a third, none of which teaches a product with either the same utility or structure as that of the invention as claimed. It is, at best, unclear what the "inherent" properties of a product combining the references of Beattie *et al.* and Chang might be and equally unclear how these would relate to any properties of the presently claimed invention given that, as discussed above, the substrate of Beattie *et al.* is porous and designed to accommodate flowthrough, the solution deposition method of Beattie is a non-impact method, the density of the array matrix of Chang is dependent on its function as an immunoadsorbent of cells, and the solution deposition mechanism of Chang is incapable of producing the array density specified in the present claims.

Therefore the Appellants respectfully submit that, unlike the situation presented in *In re* Best, the Examiner has not set forth "reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent

characteristic of the prior art." Accordingly, the Examiner is not in a position to invoke the above-quoted rule of law enunciated in Best and cases cited therein. Simply stated, it is not enough to assert that a set of prior art references which contain no motivation to combine can together inherently embody every novel aspect of the invention under examination and, based on that assertion alone, shift the burden of persuasion to the Appellants to establish that these elements are absent from a speculative combination assembled from hindsight. See *In re* Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). On this record, the Examiner cannot require the Appellants "to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on."

As such, the Appellants respectfully submit that the presently claimed invention is not taught or suggested by the cited combination of references. In view of the above amendments and remarks, reversal of the rejection is requested.

IV. Claims 16 and 36 are not unpatentable under 35 U.S.C. 103(a) over Beattie as defined by Zubay in view of Chang as applied above, and further in view of Van Ness *et al.*

Groups III and VI: Claims 16 and 36

In the prior response and reiterated herein, Appellants respectfully submit that the secondary reference does not correct the deficiencies of the primary reference. Van Ness *et al.* fails to teach or suggest a planar microarray on a slide comprising at least 1000 different polypeptides/cm^2, and wherein discrete regions have a diameter of from 20 to 200 μm. As described above, one of skill in the art would not reasonably combine the teachings of Beattie *et al.*, which require a flow-through apparatus, with the teachings of Chang *et al.*, which provide for a low-density planar array. Van Ness *et al.* fail to remedy the deficiencies of the primary references. Van Ness *et al.* teach particular coatings, but not their use in the preparation of a microarray according to the presently claimed invention.

In response to arguments presented by Appellants and reiterated herein, the Examiner states that they are not found persuasive to overcome the above rejection for the reasons stated above regarding Beattie and Chang. As these reasons have been addressed above, the Appellants respectfully submit that the cited combination of references does not make obvious the presently claimed invention and request reversal of the rejection.

V. Claims 16 and 36 are not unpatentable under 35 U.S.C. 103(a) over Barrett *et al.* (U.S. Patent No. 5,353,743, filed 13 November 1990) in view of Van Ness *et al.* (U.S. Patent No. 5,667,976, filed 14 February 1996).

Groups III and VI: Claims 16 and 36

The teachings of Barrett *et al.* are directed to a method of coating a surface with caged, photoactivatable binding members, preferably photoactivatable biotin, which can be targeted by laser or other irradiation to permit the binding of anti-ligands to defined regions on a support. Commenting upon prior techniques for immobilizing molecules on a support, Barrett *et al.* teach that "previous methods of attaching anti-ligands to surfaces are limited by low reaction efficiencies or by a general inability to regionally and selectively attach a plurality of anti-ligands to the surface," (please see column 1, lines 43-47). Critiquing a previous technique for attaching oligonucleotides to surfaces, Barrett *et al.* note that it "lacks spatial directability, and relies upon initial affinity between the photoreagent and nucleic acids prior to photoactivation" (column 2, lines 16-18). The reference articulates a "need for improved methods for attaching a broad range of anti-ligands to predefined regions of a solid support surface. The methods should efficiently provide stable attachment of selected anti-ligands to the activated surface regions, yet attachment should be restricted to the activated regions" (column 2, lines 31-34). Barrett *et al.* then teaches how to make and use reagents which permit such regionally specific, photodirectable attachment.

The Examiner asserts that it would have been obvious to combine this reference with a reference teaching a cationic film, such as Van Ness *et al.*, for the "expected benefit of convenience of attachment as taught by Van Ness *et al.* (Office Action of March 30, 2006, page 11).

However, the explicit purpose of the teachings of Barrett *et al.* is to avoid dependence upon such nonspecific attachment as that provided by electrostatic forces. The methods of Barrett *et al.* "are distinguished by the employment of novel caged binding members attached to the substrate," such that the regions of attachment may be specified and graded by photoactivation (please consult column 5, lines 33-44).

Accordingly, Barrett *et al.* teach directly against the incorporation of a method using a cationic film coating on the solid support, which would result in an inoperable invention in which the selectively photoactivatable coating of Barrett *et al.* would be rendered ineffective by the application of a universally analyte-adherent cationic film.

At best, the specifically addressable and modulatable levels of attachment described in Barrett *et al.* would then have to be accomplished by a principle different than the one described, if such were possible at all. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re* Ratti 123 USPQ 349 (CCPA 1959). Accordingly, the incompatibility of these techniques substantiates the nonobviousness of the presently claimed invention over the cited art.

Applicants additionally submit that, notwithstanding the Examiner's citation, Barrett *et al.* fail to teach a method wherein each polypeptide is at least 50 amino acids in length. As discussed above, the suggestion by Barrett *et al.* that an antibody may be of use is not equivalent in intent or form to the limitation that each polypeptide on the array be of at least 50 amino acids in length, as claimed. Barrett *et al.* place no limitations upon the length of bound molecules, stating that "typically, anti-ligands will be greater than about 100 daltons in size and more typically will be greater than about 1 kD in size" (please see column 20, line 45). Given an average amino acid mass of roughly 100 daltons, Barrett *et al.* therefore teach that anti-ligands may include amino acid monomers. Accordingly, Barrett *et al.* fail to teach or suggest a method wherein each bound polypeptide is at least 50 amino acids in length, as claimed.

Accordingly, Barrett *et al.* in view of Van Ness *et al.* fails to teach or suggest all of the elements of the claimed invention. As such, Claims 16 and 36 are not obvious under 35 U.S.C. § 103(a) over Barrett *et al.* in view of Van Ness *et al.* Reversal of this rejection is respectfully requested.

RELIEF REQUESTED

Appellants respectfully request that the rejections of Claims 10, 13-16, 18, 31 and 33-37 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance. The Commissioner is authorized to charge any fees that may be required, or credit any overpayment to Deposit Account 50-0815 order number STAN-128.

Respectfully submitted,
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CLAIMS APPENDIX

10. A microarray of discrete polypeptides on a slide, wherein each polypeptide is of at least 50 amino acids in length, wherein said microarray comprises 1000 or more discrete regions of distinct polypeptide per cm^2 of slide wherein discrete regions have a diameter of from 20 to 200 μm, produced by the method of:

(a) loading an aqueous solution of a selected polypeptide of at least 50 amino acids in length in a reagent-dispensing device having an elongate capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the solution in the channel forms a meniscus,

(b) tapping the tip of the dispensing device against a surface of a planar solid support at a defined position, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume between 0.002 and 2 nl of solution on the surface of the planar solid support, and

(c) repeating steps (a) and (b) until said microarray is formed.

13. The microarray of polypeptides according to Claim 10, wherein said polypeptides are immunological receptors.

14. The microarray of polypeptides according to Claim 13, wherein said immunological receptors are antibodies.

15. The microarray of polypeptides according to Claim 10, wherein said polypeptides are antigens.

16. The microarray of polypeptides according to Claim 10, wherein said planar solid support comprises a cationic film which binds said polypeptide.

18. The microarray of polypeptides according to Claim 10, wherein said polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure.

31. A microarray of discrete polypeptides on a slide, wherein each polypeptide is of at least 50 amino acids in length and wherein said microarray comprises 1000 or more discrete

regions of distinct polypeptide per cm^2 of slide, and wherein discrete regions have a diameter of from 20 to 200 μm.

33. The microarray of polypeptides according to Claim 31, wherein said polypeptides are immunological receptors.

34. The microarray of polypeptides according to Claim 33, wherein said immunological receptors are antibodies.

35. The microarray of polypeptides according to Claim 31, wherein said polypeptides are antigens.

36. The microarray of polypeptides according to Claim 31, wherein said slide comprises a cationic film which binds said polypeptide.

37. The microarray of polypeptides according to Claim 31, wherein said polypeptides retain the binding properties of the native polypeptide conferred by the three-dimensional structure.

EVIDENCE APPENDIX

none

RELATED PROCEEDINGS APPENDIX

None